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POLYOSTOTIC FIBROUS DYSPLASIA (ALBRIGHT'S SYNDROME)

Case Report No. 61

Dr. Ralph F. Patten

J. S., a girl aged five years and ten months, entered Children's Hospital for the first time on August 21, 1945 for treatment of an infected right toe.

The girl, the fifth of six children, was born at full term in October, 1939. All siblings were alive and well. Her mother had received sufficient treatment for syphilis. The weight at birth was $5\frac{3}{4}$ pounds (2,608 gm.). There were no immediate neonatal disturbances. The child was bottle fed and received sufficient orange juice and cod liver oil. The child gained weight and was always healthy. Her lower incisors erupted in the fifth month and she walked in the eleventh month. She was immunized against small pox at 3 months, diphtheria at 6 months and whooping cough at 9 months. The child had had no serious illness and had never required hospitalization.

The present illness began two weeks before admission at which time she "stubbed" her toe and after a few hours a blister appeared at this site. The area about the blister was badly bruised and the pain was intense at this time. Subsequently the skin over the blister became macerated and an ulcerating surface resulted.

Examination on admission revealed a well developed, slender girl in no acute distress. Pigmentation of the skin was not observed. Examination of the right leg revealed several excoriations over her tibia. The first toe showed a raw lesion which was discharging thin watery pus. The tibia was prominent and sharp along its anterior border. There was no evidence of precocious sexual development. The remainder of the physical examination was essentially negative.

Laboratory Data

The hemoglobin content varied from 8.5 gms. to 11 gms. on five different examinations during the child's hospital stay. The white blood cell count was 4,500 with a differential of 45% neutrophils, 42% lymphocytes and 13% eosinophils. Subsequent white-counts revealed a persisting eosinophilia ranging between 7% to 14%. The level of serum calcium varied from 9.5 mgm. to 11.4 mgm. % and that of inorganic phosphorus from 2.2 to 6.2 mgm.%. The alkaline phosphatase was 6.6 King-Armstrong units, while the acid phosphatase was 29.97 King-Armstrong units. The serum protein was 6.00 gms. per hundred cubic centimeters. Values for blood cholesterol, sugar and non-protein nitrogen proved to be well within the

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normal range. The sedimentation rate was normal. Examination of the urine was repeatedly negative. There was no Bence-Jones protein in the urine. The Sulkowitch test showed no precipitate.

Roentgenograms of the skeleton revealed the right tibia and fibula to be riddled with many small cystic areas. These areas appeared to be located

FIG. 1. J. S. NOTE MULTIPLE CYSTIC LESIONS IN TIBIA AND FIBULA DUE TO FIBROUS DISPLASIA

for the most part in the lower half of both bones, were non-expansible, and were not surrounded by an increase in bone formation. There was very little soft tissue or periosteal reaction about the lesion. Examination of the left upper extremity revealed the presence of an area of decreased density in the medial aspect of the distal head of the humerus.

On October 8, the anterior surface of the tibial shaft was exposed at operation. The bone surface was slightly discolored and hemorrhagic.

A large wedge of bone was removed for microscopic study. Histologic examination revealed a number of marrow spaces containing well organized fibrous tissue. No normal bone was seen and the spaces did not contain any cellular structure. A few well differentiated bone trabeculae were seen.

The child was discharged from the hospital November 30, 1945 with the lesion about the toe healed. She is now being followed in the orthopedic clinic.

ETIOLOGY

The cause of Albright's syndrome has not been settled. However, most investigators believe the condition, as a whole, represents a congenital anomaly of development, involving many types of tissue.

Albright's[1] original communication advanced the suggestion that the peculiar distribution of the osseous and cutaneous lesions seemed to exclude the possibility of a metabolic or endocrine disturbance as the primary etiologic factor. A neurologic defect seemed more probable and the gonadal dysfunction was postulated as being due to a disturbance of afferent impulses to the pituitary gland. In 1938 Albright et al. published two cases occurring in the male both of whom showed an absence of the cremasteric and abdominal reflexes on the side corresponding to the bone lesions. Ford and Guild[2] lent further support to Albright's theory by pointing out that injuries involving the region of the hypothalamus may produce sexual precocity. These investigators observed precocious puberty following measles, encephalitis and epidemic encephalitis. It might be claimed that Albright has explained only one part of his syndrome and has failed to explain the important bone lesions and cutaneous pigmentation.

Moehlig and Schreiber[3] believe that there is a hereditary basis for the disorder. The maternal side of the patient's family were often short statured individuals with early dental decay. This they attributed to an hereditary defect in the bone forming mesenchyme. However, this explanation seems untenable in view of the fact that it is impossible to explain the unilateral distribution of the osseous lesions on the basis of a chromosomal aberration.

Primary hormonal imbalance has been postulated by several investigators. Helfet[4] was of the opinion that in Albright's syndrome there existed chronic hyperparathyroidism. This was based on the frequent finding of a mild increase in serum phosphorus in these cases and it was suggested that by using the acetates and gluconates of aluminum the amount of phosphorus could be reduced by precipitating a part of it in the intestine.

Sternberg and Joseph[5] submitted autopsy evidence to show pathologic

changes in the endocrine glands. The patient had been studied by McCune [6] and had died of a complicating bronchopneumonia. The pituitary gland showed a hyperplasia of the basophilic elements with adenomas of microscopic size. The basophilic cells were larger than normal and definitely on the pleomorphic side. These changes were interpreted as evidence of malfunction. The thyroid gland showed microscopic adenomas of the fetal type. The patient has a long history of toxic diffuse goiter. The thymus showed hyperplastic changes. The ovarian tissue showed multiple follicular cysts with an absence of maturing corpora lutea. The adrenal cortex showed definite atrophy while the medulla was hypertrophied. The parathyroid glands were normal in appearance. Macroscopically and microscopically no lesions in the brain, especially in the hypothalamic region, were demonstrated. On the basis of these findings, Sternberg and Joseph found it difficult to accept the theory of multiple congenital defects of development and they postulated an endocrine basis for Albright's syndrome. In this case, it was thought that a diffuse toxic goiter was responsible.

There are several other cases in the literature which presented symptoms of hyperthyroidism. However, the large majority of cases do not have such symptoms. With the changes in the pituitary some investigators have considered "the master gland."

Clinical Features

Incidence as to age and sex: It must be admitted that the bizarre outspoken examples of extensive bone lesions, huge areas of pigmentation and menstruation in the early years of life is of rare occurrence. The incomplete form, in which only one or two of the triad of symptoms are present, is not uncommon. Jaffe [7] has seen 23 cases of polyostotic fibrous dysplasia. A total of 59 cases of this disease has been reported, 39 of the complete and 20 of the incomplete variety. This includes the case described herein.

In regard to incidence by age, the impression is gained that severe involvement may become clinically manifest in adolescence or even as early as childhood. This is true in the complete form. In the incomplete form the patient may be in the third or fourth decade before clinical symptoms appear.

The disease apparently has a tendency to occur in women, the ratio of women to men being 3 to 2. This ratio is interesting since it is the same relationship that exists in parathyroid adenoma.

Clinical Manifestations

The disease may be present in a patient for some years before it is discovered. The common clinical signs and symptoms are pathologic frac-

ture, limp, pain and deformity of the affected limb. Usually, the first symptom to attract attention is a spontaneous fracture which leads to x-ray examination of the bones. In our case the lesions were discovered accidentally. Generalized "bone pains" so characteristic of hyperparathyroidism are absent. However, local pain may be present due to an expanding tumor or fracture. Patients may seek treatment also because of shortening of a lower extremity, cox vara, bowing of the femur or deformity of an upper extremity.

Precocious puberty is a cardinal symptom in the complete form and it is almost exclusively limited to females, particularly in those in whom osseous lesions are extensive. The parents often relate that the child started menstruating at an early age or developed secondary sex characteristics prematurely.

Along with sexual precocity there may be pronounced acceleration in somatic maturation. The bone age may exceed the chronologic age of the patient in that there is premature maturation of the epiphyses. Also the epiphyses unite early within the diaphyses. As a result it has been found that adult females are of short stature.

The presence of hyperpigmentation of certain areas of the skin is the other symptom of the triad of Albright in its complete form. The most frequent sites are sacrum, buttocks and upper back. Unilateral involvement is apt to be accompanied by pigmented spots on the same side of the body, and bilateral involvement shows the same distribution as the bony lesions. However, this is not always the case. The patches of pigment may be easily missed. The disease is chronic as its symptoms and osseous lesions indicate.

Distribution of Osseous Lesions

The osseous lesions tend to be exclusively or predominantly unilateral. However, bilateral lesions also occur. The lesions are scattered, localized and multiple. This is in sharp contrast to osseous manifestations of hyperparathyroidism. Usually the bones of the lower extremities are affected more than those of the upper extremities. A combination of the upper and lower extremity involvement is not infrequent.

The long bones of the extremities are affected in the following order of frequency; femur, tibia, humerus and radius. Next in frequency are the bones of the skull, pelvic bones, ribs and phalanges. Rarely, the fibula, clavicle and spine are involved.

Laboratory Data

Chemical findings in the blood: Serum calcium and phosphorus determinations are usually normal, one of the important diagnostic points in differentiation from hyperparathyroidism. In a few cases a slightly ele-

vated calcium level has been reported. Calcium excretion may be normal or occasionally increased. The phosphatase level is frequently elevated indicating osseous activity.

Several cases have been reported in which the serum cholesterol was elevated. This determination resulted in the diagnosis of xanthomatosis. Later, biopsy of these cases revealed characteristics of polyostotic fibrous dysplasia.

Roentgenologic Characteristics

The diagnosis of Albright's syndrome in its complete form can often be made by x-ray studies. However, it may be very difficult to make such a diagnosis in some cases, especially where solitary lesions of bone exist. As previously noted, the lesions are usually unilateral, scattered and localized. Normal bone is present between the regions of abnormal bone. The objective findings may be summarized as follows: broadening or expansion of bone; thinning of the cortex; areas of decreased density of a trabeculated appearance, often erroneously diagnosed as "cystic disease"; absence of involvement of the epiphyses; presence of normal bone in a considerable portion of the skeleton; secondary deformities of affected bones; sometimes, abnormally long bones; sometimes, premature union of the epiphyses.

Lesions of polyostotic fibrous dysplasia consist mainly of the replacement of the medullary structures with fibrous tissue. This process leads to thinning of the cortex from within. In many cases there is moderate expansion of the bone. On the other hand, the lesions may begin subperiosteally and cause erosion of the cortex. In these cases there is very little increase in width of the bone.

Since there is replacement of the medullary substance by masses of fibrous tissue, the involved structures show cystic-like figures by roentgenologic studies. This explains why in many cases the condition is clinically mistakenly diagnosed as Recklinghausen's disease. Also, if the attention is focused on a single bone without roentgen examination of the other parts of the skeleton, an erroneous diagnosis of giant cell tumor, localized cyst of the bone, or even endochondroma may be made.

As a result of the formation of fibrous tissue in the bone, there occurs pathologic fractures. The rapid healing of the fracture indicates that the reparative process proceeds in an orderly fashion. Pathologic fractures often result in shortening and gross deformity of bone. Cox vara and bowing of the femur or of the tibia are common deformities.

In Albright's syndrome the bones may be abnormally long, that is, the age of bone exceeds the chronological age of the patient. Premature arrest of growth, which is manifested by union of the epiphyses, may result in dwarfism.

Lesions of the skull are frequently seen. The changes in the occiput and mandible have the same appearance as lesions seen elsewhere. Osteosclerosis is an infrequent finding. The basal portion of the frontal bone and sphenoid, ethmoid and maxillary bones are different from lesions of polyostotic fibrous dysplasia, in so far as osteosclerosis is present. Complete obliteration of the paranasal sinuses is frequently seen as well as ocular proptosis. Asymmetry of the skull may lead one to suspect the condition. The term leontiasis ossea is used to designate a type of generalized facial deformity.

Pathologic Picture

Since few patients succumb from polyostotic fibrous dysplasia, there is very little necropsy material for study. Thus it is necessary to reconstruct a comprehensive picture of the osseous lesions from biopsy specimens. Thinning of the cortex, which is due to resorption and erosion of the endosteal surface by the masses of the fibrous tissue, is a constant finding. There is no periosteal deposition of new bone unless there has been a recent fracture. The substantia spongiosa and marrow is replaced by fibrous tissue which may be vascular or avascular. This fibrous tissue is composed of spindle cells with pale staining nuclei. The underlying connective tissue may be fairly cellular in some areas and acellular in other areas.

Dispersed within the fibrous tissue are small trabeculae of primitive poorly calcified bone. These trabeculae tend to be very sparse in avascular tissue. Jaffe believes that these trabeculae developed by osseous metaplasia without the mediacy of osteoblasts. There is very little bone resorption as is indicated by the paucity of osteoblasts. Scattered in vascular tissue are granules of hemosiderin representing previous capillary hemorrhage. Cysts are not found except in cases in which degenerative changes have occurred. Foam cells are seldom seen and their presence makes it necessary to differentiate the condition from xanthoma of bone. Scattered in the fibrous tissue, one may find nests of giant cells which resemble osteoclasts. They are basophilic and contain 10 to 20 nuclei.

Most investigators are of the opinion that the diagnosis of Albright's syndrome cannot be made by biopsy of bone alone. The interpretation of the biopsy should be considered in conjunction with the clinical history, laboratory studies of the blood and x-ray studies. Biopsy studies of the pigmented areas of the skin reveal an excess of melanin in the stratum germativium. Sometimes this pigment is also found in the granulosa cells.

Differential Diagnosis

Hyperparathyroidism is the main disease that must be differentiated. No less than 20 cases have been explored without finding an adenoma of

the parathyroids and five of these patients were subjected to 2 operations. Precocious puberty in the complete form of Albright's syndrome is an important diagnostic point. Then, too, hyperparathyroidism is rare in children and roentgenograms show generalized decalcification of all bones and skeleton. This is in contrast to Albright's syndrome which begins in childhood and x-ray shows the lesion to be unilateral, localized and multiple. Generalized bone pain which is found in hyperparathroidism is absent in Albright's syndrome. Muscular weakness and digestive disturbance are frequent complaints of hyperparathyroidism. Cysts are the exception rather than the rule in Albright's syndrome. Hypercalcemia, hypophosphatemia, and hypercalcinuria are the usual findings in parathyroid adenoma. The values for serum calcium and phosphorus are usually normal in Albright's syndrome. Blood phosphatase is usually elevated in both conditions. In a few equivocal cases in which the osseous lesions are not definite by x-ray studies and in which the blood calcium and phosphorus are elevated, a biopsy should be done before exploration of the parathyroids.

In an occasional case unilateral involvement may be mistaken for dyschondroplasia or Ollier's disease. In his original paper, Albright declared that Ollier's disease can be readily differentiated in view of the absence of precocious puberty and pigmented areas. Other differential features are the fact that dyschondroplasia does not affect the bones which are laid down in membrane and there is involvement of the epiphyses. As previously noted, fibrous dysplasia may affect the bones of the skull and does not touch the epiphyses. Thus, Ollier's disease can be differentiated by the clinical history and roentgenograms.

Von Recklinghausen's neurofibromatosis shows a striking resemblance to polyostotic fibrous dysplasia, especially in so far as there may be pigmentation of the skin and osseous lesions. Some writers believe that the syndrome is an example of "atypical neurofibromatosis." However, a biopsy showing neurofibroma immediately eliminates fibrous dysplasia.

Xanthoma of bone may superficially resemble Albright's syndrome. This is especially true in cases in which the cranium is involved. Usually, however, the blood cholesterol is elevated. In those cases of Albright's triad in which the cholesterol is elevated, a biopsy will settle the diagnosis. Foam cells with a distinct lipid are present in large numbers.

Paget's disease is readily eliminated because the age of onset in this disease is much later and biopsy specimens show the characteristic mosaic pattern.

Osteogenesis imperfecta can be excluded on the basis of blue sclera, hereditary tendencies, biopsy specimens and x-ray studies.

Multiple hemangiomas of bone may produce widespread osteolytic lesion of the skeleton; however, a biopsy will help settle the diagnosis.

Various other conditions capable of producing precocious puberty must be differentiated. Granulosa cell tumors produces none of the other manifestations of Albright's syndrome. The same may be said of tumors of the adrenal medulla and pituitary gland.

Prognosis and Treatment

The long duration of symptoms is an indication of the chronicity of the disease and the slow progression of its osseous lesions. Studies indicate that in older patients there may be less evidence of activity of lesions. Since it is a chronic disease and since the cause is not really known, the prognosis should be guarded. Recurring fractures frequently cause deformities.

Unfortunately there is no specific treatment. Helfet recommends the use of acetate of aluminum especially in cases of extensive osseous involvement. However, the results have not been particularly noteworthy.

Vitamin D and calcium administration does not produce any beneficial effect. Roentgen irradiation in small or moderate dosage may be tried empirically. However, this treatment is contraindicated in widespread lesions and in growing children as this may lead to arrest of growth. Also it should be borne in mind that x-ray in large doses may cause necrosis of the thinned cortex and lead to pathological fractures.

Pathologic fractures should be splintered in the usual manner. In cases in which there are large cysts and in which there is delay in healing, bone grafts may be tried.

Summary and Conclusions

1. One case of incomplete form of Albright's syndrome which lacked precocious puberty and skin pigmentation is presented.

2. The cause of the syndrome is unknown. The theory of a congenital developmental defect involving many tissues is supported by some investigators. Others believe that a primary hormonal disturbance involving one or several of the endocrine glands may account for the triad of bone lesions, skin pigmentation and precocious puberty. Albright's suggestion of an embryonic defect in the region of the hypothalamus is an interesting hypothesis. Until the true etiology is discovered, it has been proposed to designate this bizarre condition as Albright's syndrome.

3. The importance of being familiar with Albright's syndrome in both the complete and incomplete form is emphasized in differential diagnosis of hyperparathyroidism. No less than 20 cases have been subjected to exploratory operations of the parathyroid glands.

4. The syndrome may be diagnosed by: a. a complete history; b. chemical studies of the blood; c. roentgenological examination of the entire skeleton; d. biopsy of a suspected lesion.

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HEMOPHILUS INFLUENZA EPIGLOTTITIS

Case Report No. 62

Dr. Charles Stiegler H. H. 46-3475

H. H., a 13 month old colored male, was brought into the dispensary of Children's Hospital at approximately 3:15 p.m. on May 3, 1946, at which time his respirations were extremely labored with severe suprasternal and supraclavicular retractions. While being carried into the examining room, his respirations ceased; artificial respiration was administered, and the tongue was pulled forward. Oxygen by open funnel and adrenalin, ½ cc. intramuscularly, were administered as quickly as possible, with a return of spontaneous respiration, though labored and irregular. The nasopharynx was aspirated yielding a moderate amount of fairly thick, white mucous. With the tongue secured in a forward position, an examination of the throat revealed diffuse redness and edema of the epiglottis.

The child had been well until the previous day, when he seemed to develop a "slight cough, runny nose, and a little hoarseness" towards evening. He slept well throughout the night, but shortly after awakening, his respirations became somewhat rapid and progressively more labored on up to the time of admission to the dispensary.

In view of the rapidity of the onset, the epiglottitis, and the severe respiratory embarrassment, it was believed that there was probably an associated laryngeal obstruction due to edema and inflammation on the etiological basis of either an H. influenza or streptococcal infection. Preparations for laryngoscopy and a tracheotomy were made at once.

At 3:45 p.m., ½ hour after admission, direct laryngoscopic examination by Dr. Allan Walker revealed extreme edema of the cords; a #3.5 tube could not be passed. The suction tube was passed, attached to oxygen, and a tracheotomy was done under local anesthesia with the insertion of a #1 tracheotomy tube. The operation was completed at 4:15 p.m.

Upon being transferred to the medical ward, the patient was placed in an oxygen tent; his respirations were labored but fairly regular, and aspiration through the tracheotomy tube yielded only a small amount of thin, blood tinged mucous. A culture and direct smear were taken through the tracheotomy tube, following which therapy was initiated.

Because of the gravity of his condition and an as yet undetermined etiological organism, it was deemed advisable to employ all the therapeutic measures at hand. Penicillin, 40,000 units intramuscularly stat followed by 20,000 units every 3 hours was administered. The patient was then given two ampoules of H. influenza antiserum intramuscularly. Sodium

sulfadiazine, estimated at 2½ grains per pound of body weight in 24 hours, was administered by clysis on a six hour divided dosage schedule after an initial dose of twenty grains.

At 7:00 p.m. on the day of admission, the respirations had become considerably less labored. The direct smear of the tracheal exudate was reported at this time as showing numerous organisms morphologically resembling H. influenza. Accordingly an additional three ampules of H. influenza antiserum were administered intramuscularly.

By the following day a marked degree of improvement was apparent. There was only slight retraction on inspiration although the respiratory rate remained rapid. A portable chest film was taken which showed the trachea, heart, and mediastinum to be shifted to the right; lung detail was lacking but there appeared to be a partial atelectasis of the right upper lobe and possibly a partial atelectasis of the left lung. The patient was taking liquids well by mouth. The sulfadiazine blood level was 11.6 mgm.%. The culture of the tracheal exudate taken the previous evening showed H. influenza and non-hemolytic staphylococcus albus. The temperature, which ranged between 102–103° the day of admission, now ranged between 101–102°. Although the patient continued to show improvement during the next 24 hours, another ampoule of H. influenza antiserum was administered on May 5th.

On the following day, the patient was able to take an oral solution of sodium sulfadiazine and the clyses were discontinued. Throughout the first week of his hospitalization, periodic sulfadiazine blood levels revealed that a concentration of 15–20 mgm. % was being maintained. A second culture of the tracheal exudate on May 6th again grew out H. influenza. On May 8th, five days after admission, the tracheotomy tube was removed because it was becoming obstructed by dried exudate; as the patient showed fairly marked respiratory distress, a clean tube was reinserted. The patient had an unexplained temperature elevation of 101–102° on May 8th and May 9th and another ampoule of antiserum was administered. The temperature fell slowly to normal range over the next two days, and he remained afebrile during the remainder of his hospital course.

The tracheotomy tube was removed on May 12th and the wound edges were approximated with adhesive tape. After a few hours, during which the respirations were slightly labored, the patient became acclimated and quiet. Oxygen was discontinued May 14th. A chest film taken at this time showed the heart to be somewhat enlarged to the left. There was no evidence of atelectasis at this time and the heart and mediastinal contents were in their proper position. There was no evidence of pathology of the parenchyma.

Sulfonamides were discontinued May 20th and penicillin was discon-

tinued 4 days later. During the subsequent 24 hours, the patient's temperature rose steadily, reaching 104°. The respirations were rapid with mild retractions, but physical examination was otherwise negative. The tracheotomy wound was healing well without evidence of secondary infection. Penicillin therapy was started again and was followed by a prompt defervescence of temperature to normal and subsidence of the respiratory symptoms during the next 24 hours. Penicillin therapy was discontinued 6 days later without occurrence of further symptoms. The patient was discharged from the hospital on June 6th after an uneventful subsequent course.

Discussion

This case of H. influenza epiglottitis is presented because it raises several points of interest, the most important being an appreciation of its emergency nature. The diagnosis should be suspected in any case of fulminating respiratory distress preceeded briefly by a mild upper respiratory infection, with or without a history of hoarseness and a croupy cough. When the diagnosis is under consideration, examination of the patient should be made as brief as possible, preferably with facilities at hand for an emergency tracheotomy if the occasion arises. The markedly congested pharynx and the swollen cherry-red epiglottis in the presence of suprasternal, supraclavicular, and abdominal retractions will usually suffice to establish an admission diagnosis. Examination of the lungs will reveal an absence of diffuse rales, such as would be heard in the presence of an interstitial pneumonia or a disseminated bronchopneumonia. The causative organisms in the cases occurring in this hospital have been either H. influenza bacillus or hemolytic streptococcus.

Because of the seriousness of this condition, we feel that prompt vigorous treatment is indicated. Although cases of recovery without tracheotomy have been reported in the literature, conservative "watchful-waiting" has not been very successful in the cases here. We believe that tracheotomy is indicated in the presence of moderate to severe respiratory distress in these cases, without relying too strongly on chemotherapy and specific antisera until an artificial airway has been established. Although a tracheotomy was performed promptly in this case, the question arose as to whether we might not have begun the administration of penicillin and H. influenza antisera while preparations for the operation were being made. Since these patients with laryngeal obstruction are prone to develop laryngospasm when disturbed, it is probably more discreet to wait until after the tracheotomy has been performed and smear and culture obtained for laboratory examination before instituting therapy.

After an artificial airway is established, cultures and smears may be

taken from the pharynx and the trachea. Following this we believe therapy consisting of penicillin, sulfonamides and H. influenza antiserum is justified until an etiological organism is established. Not infrequently, an adequate direct throat smear may reveal the nature of the causative organism quickly and will predicate the therapy to be used. The recommended initial dose of H. influenza antisera is 4-6 ampules (25 mgm. per ampule of the antibody), depending on the severity of the case. Sulfadiazine should be given in sufficient dosage to maintain a blood sulfadiazine level of 15 mgm. %. Penicillin is administered to help control or prevent the growth of secondary invaders.

The exclusive services of a nurse experienced in caring for a tracheotomy case is almost indispensable.

The subsequent course will determine whether or not additional antisera is to be given, the average quantity administered usually varying between six and ten ampules.

SALICYLATE INTOXICATION WITH RESULTING SEVERE KETOSIS: REPORT OF TWO CASES

Case Report No. 63

Dr. Clifford J. Tichenor

D. D. 45-6198
W. P. 45-6252

These brief reports of salicylate dyspnea and acidosis are presented in order to point out that aspirin intoxication can occasionally occur in children being treated ostensibly with a therapeutic antipyretic dosage of the drug. It is well known that salicylism may result during the course of treatment for rheumatic fever, employing relatively large doses, but it is not generally appreciated that a hypersensitive child may incidentally develop ketosis from ingestion of seemingly insignificant amounts of aspirin.

Case #1

D. D., a white male, age 4 years, had a history of a fever of unknown origin of two weeks duration. Three days prior to admission to Children's Hospital the patient was placed on a daily dose of four grains of aspirin initially and when the fever did not subside in the next 2 days, the dose was increased to 8 grains per day. Shortly thereafter he became drowsy and nauseous and appeared quite listless. On the day of hospitalization he was noted to be breathing heavily with rather slow deep respiratory excursions.

Physical examination revealed typical Kussmaul acidotic breathing but otherwise was essentially negative.

The blood count showed a hemoglobin of 10.5 grams, with 3,910,000 red blood cells. The white cell count was 10,400 with a normal differential. The urine was slightly cloudy and alkaline with a specific gravity of 1.016; there was 200 mgm. % of albumin and a 4 plus acetone; the urinary sediment was negative. The carbon dioxide combining power was 22 volumes % on admission while the blood sugar was 125 mgm. %.

Four hundred cc. of M/6 lactate solution was given intravenously shortly after entry and was repeated in six hours, resulting in rapid clinical improvement. A carbon dioxide combining power taken the following day was 36 volumes %. Recovery was uneventful.

Case #2

W. P., a white male, age 2 years, had been treated for almost two weeks by a private physician for an upper respiratory infection. Since this illness did not seem to be responding to sulfonamide therapy, a mixture con-

taining 2½ grains of aspirin and ½ grain of Dover powders was prescribed every three hours. The parents were uncertain as to the exact number of doses given. Three days later the child was noted to have marked respiratory hyperpnea which was the chief clinical feature presented at the time of admission.

Physical examination revealed a pallid, dehydrated, cyanotic child who was semi-comatose. Respirations were rapid and deep with characteristic acidotic breathing. There was no acetone odor detected on the breath. The remainder of the examination was not remarkable.

The blood count showed a hemoglobin of 6 grams with 3,690,000 red blood cells. The white cell count was 7,600 with a normal differential. There was variable achromia, moderate microcytosis and anisocytosis. The urine was clear with an acid reaction; the specific gravity was 1.020 and contained only a trace of acetone. The blood sugar was 83 mgm. %, the non-protein nitrogen 37 mgm. % and the carbon dioxide combining power 18 volumes %. A salicylic acid blood level taken one day after admission was 25 mgm. %. Two hundred cc. of M/6 lactate was given intravenously, followed by 200 cc. 5% glucose in Hartman's solution subcutaneously. A second intravenous of 150 cc. of M/6 lactate was given six hours later.

On the following day the carbon dioxide combining power was 32 volumes % and the clinical improvement was noteworthy. The respiratory rate had dropped from sixty to twenty-five per minute and the child was alert and active.

Discussion

When a moderately large dose of a salicylate is given, ringing in the ears, perspiration, dimness of vision, confusion and dullness are produced. After excessive doses, pain in the throat and abdomen, vomiting, dysphagia, diarrhea, dyspnea, subnormal temperature, coma and convulsions supervene and death from respiratory paralysis may occur.

The fatal dose, in acute cases, is hard to estimate, but quantities of 4 to 10 grams have caused death at times. Many individuals are susceptible to the drug to an abnormal degree and react unfavorably with a small dose, while others can take a large dose without ill effects.

It is the sensitive individual, however, in whom symptoms are produced rapidly. The acid-base balance of the blood is disturbed by aspirin intoxication, the first change probably being an acid deficit alkalosis due to the marked respiratory hyperpnea, which in turn is believed to be due to central stimulation by the drug. This would result in an increased pH and followed by a striking and persistent ketosis.

It has been suggested that the salicylates have a specific inhibitory effect

on carbohydrate metabolism and thus the carbon dioxide deficit type of alkalosis may be reversed by the development of the ketosis, and if severe enough, by a true metabolic acidosis. This determination, however, should be established by the pH of the blood and not by the carbon dioxide combining power alone.

It is recommended that normal saline be used to combat dehydration and that M/6 lactate be used for the ketosis. Lactate is easily oxidized when salicylate intoxication is present so that many times the usual calculated amount of lactate may be necessary to combat the low carbon dioxide combining power of the blood.

It is recommended that acidosis be established by a pH of blood to avoid administration of alkali to a child with a respiratory alkalosis. Large amounts of glucose given intravenously will help correct the ketosis and also aid in the excretion of salicylates. Sedatives such as phenobarbital may help in reducing excitability and hyperpnea. Oxygen may be used to protect against the obvious dangers of anoxia.

Conclusions

1. Parents should be questioned concerning the sensitivity of the child to salicylates.

2. Small doses of aspirin can produce respiratory hyperpnea and ketosis in the hypersensitive child.

3. Careful clinical observation of the patient is necessary when aspirin is prescribed.

4. Possible hazards in the administration of salicylates, even in small amounts, should be borne in mind to preclude its indiscriminate use.

5. The onset of hyperpnea without an apparent cause after administration of aspirin should call to mind the possibility of salicylate intoxication.

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BILATERAL RETINOBLASTOMA

Case Report No. 64

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S. McF. 44–9067

S. McF., a two year old colored male, was brought to the Eye Clinic in February, 1946 because his mother had seen a "white pupil" on the left side. The child had an attitude of blindness. Because the white mass extended to the back of the lens and the lens in front of it was entirely clear and the anterior segment was normal, the chances of its being a retinoblastoma were high, and the child was admitted for enucleation of a blind eye that was probably the site of a retinal tumor.

Examination under ether anaesthesia before operation disclosed a large, fluffy, white, spherical tumor, 11 diopters high, with a fluffy, satellite mass above in the right eye. There was no mistaking the appearance of this tumor, arising from the posterior pole and almost covering the disc, for anything except a retinal tumor. Shortly after enucleation of the lefteye, radiation therapy was begun and the tumor showed such radiosensitivity that by May 8th it was seen to be small and round and about four diopters high with considerable normal fundus surrounding it. At this time the child had obviously better vision.

When it was known that tumor cells were in the nerve beyond the point of resection, the child was recalled but by that time there was an obvious recurrence of tumor in the left orbit. The child was readmitted to Children's Hospital for the purpose of expediting radiation therapy to the recurrence. A maximum amount of radiation, 225 R over 42 square centimeters, was given to the left side daily by Dr. Caulk at the Warwick Clinic, and the radiation of the right retinal tumor was postponed. On June 13th, this tumor was seen to be elevated seven diopters and gave the appearance of being more elongated than when seen previously.

Pathology

The tumor in the left eye was a large celled tumor arising in the retina, but showing no rosettes. It had invaded a considerable area of the choroid and large clumps of the tumor cells were seen in the cross-section of the excised nerve.

Discussion

Retinoblastoma occurs in about one case in 34,000 births. They appear as sporadic cases which may be unilateral or bilateral with a familial inci-

dence, which cases are usually bilateral. The number of bilateral cases is usually given as 15 to 25%, but in some series it may run as high as 50% or more [1, 10]. The bilateral cases are said to be higher in the genetic type than in the sporadic. Griffith and Sorsby [2] suggest that there are possibly two types of retinoblastoma and that it behaves as an irregular dominant. Cummings and Sorsby [3] advise that the unilateral sporadic retinoblastoma originates in the outer nuclear layer, while bilateral tumors are derived from both nuclear layers. In their studies the hereditary tumors did not differ in type from the sporadic bilateral tumors.

The classical treatment of retinoblastoma has always been enucleation, but the percentage of cures after this treatment is 35 to 40%. Therefore, there have been attempts to improve the treatment both from the point of view of surgical technique and radiation therapy. Dott and Meighan [4] performed an intracranial resection of the optic nerve in glioma retinae, reported in 1933. Ray and McLean [5] and Shannon, Jaeger, and Forster [6] developed a combined intracranial and orbital operation for retinoblastoma. The latter were the first to use it on a bilateral case. The bone flap is prepared as for a hypophyseal approach and the frontal lobe is lifted up. The optic nerve is resected and the foramen and a bit of temporal muscle tissue is used to plug the foramen. Thirteen days later enucleation is performed with all the optic nerve and sheath delivered by traction after the extraocular muscles are severed. This is much more satisfactory than an exenteration of the orbit, which even though followed by prompt irradiation falls short of cure in 15 to 20% of cases. A. F. deRoetth [7] reported electrocoagulation of two cases as in a retinal detachment operation, which he used in the State Eye Hospital in Budapest. One was successful. Radon seeds have been used [8].

The most encouraging development in recent years has been the treatment of retinoblastoma by combined surgery and radiation, by Martin and Reese at Memorial Hospital in New York. Their first report was in 1936 and two progress reports followed in 1942 [9] and 1945 [10] with follow-ups on twenty-four cases. They gave fractional doses of 14,000 to 16,000 R to the tumor in the second eye after enucleation of the first, or worse eye. They used a temporal portal and one directed across the bridge of the nose. No radiation could be allowed to go through the anterior chamber without risk of serious complications. They consider that the growth is bilateral in the majority of cases. In their twenty-four cases the second tumor was seen at first in only fourteen cases, and the second tumor was found from one to twenty-six months later in the other cases. They consider that these tumors have multiple origin. Of the first nine cases, two patients were left without recurrence and with vision. Four were living, but blind. In fourteen subsequent cases there were three failures; three partial failures,

patient living but blind; but eight, or 57% of patients were living with freedom from disease and with vision. They also consider that if the tumor reached the choroid it was uncontrollable by radiation.

C. H. Hu [11] in 1930 reported two cases from the Peking Union Medical College with four post mortems. One of these showed metastases to the eye lids, opposite optic nerve, meninges, spinal cord, bones of face, ribs, scapulae, sternum, humeri, femur, calcanei, vertebrae, muscles, including the supraspinatus, gluteus medius, and iliopsoas, lymph nodes, pleura, and parotid gland. The second case, in which the tumor was found in the choroid with the sclera intact, revealed tumors in the brain, spinal cord, choroid plexus, and the right optic nerve was surrounded by tumor. He also quoted the literature as showing metastases to the brain and meninges, skull and bones of face, neighboring lymph nodes, parotid gland, skeletal bones, liver, cord, and meninges, kidneys, ovary, lung, spleen and testes, the frequency of incidence in the order given.

Summary

We have here a child in whom bilateral retinoblastoma was well developed before he was first seen with the tumor in the worst left eye extending into the choroid and nerve, and was inadequately removed by classical enucleation. The tumor has shown itself to be radio-sensitive but it is highly malignant and apparently increasing beyond the control of such radiation as has been given at the late date at which it was instituted. To do anywhere near an adequate surgical removal now would demand an orbital exenteration and cutting of optic tracts behind the chasm. It is possible that there would even then be metastases to other organs. The question presents itself as to whether treatment should be continued or discontinued because the prognosis by every criterion seems hopeless.

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CLINICO-PATHOLOGICAL CONFERENCE

Directed by Dr. E. Clarence Rice
Assisted by Dr. Robert B. Sullivan

Case Report No. 65

Dr. Robert B. Sullivan M. P. 35–3202

M. P., a ten year old colored girl, entered the hospital because of a "growth on the jaw" which had been first noticed one week before. Three days before admission she had been seen in the dispensary because of an itching nose, a cough, and difficulty in breathing. The only positive findings of that time were an oral temperature of 100°, reddened turbinates, and a hard, nodular, non-tender swelling on the left mandible which caused no discomfort. She was admitted in order to investigate this mass.

In the past there had been a moderate number of visits to the dispensary because of colds and minor ailments. She had had measles, mumps, chicken pox, and pertussis but no serious illness or any operations. The parents and four siblings were healthy.

When admitted, the child's temperature was 100.2°. She was well developed but undernourished. The left submandibular and cervical lymph nodes were slightly palpable. An indurated bony mass was felt over the middle of the body of the left mandible without signs of acute inflammation or tenderness. The left lower second molar tooth was absent. An x-ray examination of the mandible revealed the presence of a large cystic area involving the left ramus and shaft measuring 6.0 by 3.5 cm. The second molar had been dislocated and was lying loose on the floor of the cyst. There was extension to the roots of the first molar and the left lateral incisor. No other positive findings were elicited. The hemogram and urinalysis were normal. Both the Kahn and tuberculin tests were negative. The blood phosphorus was 4.5 mgm. % and the blood calcium was 11.0 mgm. %. The alkaline phosphatase was 14 King-Armstrong units. Other x-ray examinations revealed no abnormality of the right mandible. There was an opacity over the anterior ethmoids, some haziness over the frontal sinuses, and the remaining nasal accessory sinuses revealed no evidence of abnormality. The sella turcica was normal as were the bones of the upper and lower extremities.

During the two weeks of hospitalization she was asymptomatic except for a low grade daily fever. A cystectomy was decided upon. The anaesthesia was nitrous oxide and oxygen with ether being added. A French endotracheal catheter #26 was in place and respirations were free. An incision was made along the left lateral mandibular ridge intra-orally and

the gingiva partially reflected. Suddenly respirations ceased and at the same time a supra-clavicular emphysema appeared and spread rapidly.

Postmortem examination disclosed a massive subcutaneous emphysema extending from the mandible to the mid-thigh region. There was a marked mediastinal emphysema and 50% pneumothoraces bilaterally. Similarly there was a massive pneumoperitoneum and retroperitoneal emphysema. The right auricle and ventricle were greatly dilated and there was congestion of the abdominal viscera. Cultures from the larynx and lung grew

FIG. 1. M. P. Lateral x-ray of the mandible showing the large cystic area in the jaw with the dislocated tooth lying on the floor. The x-ray appearance is that of a dentiduous cyst.

Streptococcus viridans but those from the heart's blood and spleen were negative. Microscopic examination of lung tissue revealed atelectasis and congestion with possibly some increase in the perivascular connective tissue. No evidence of interstitial emphysema was seen in the sections examined. Unfortunately we have no section from the mandibular cyst, but the probability is that it was either a follicular cyst or an adamantine epithelioma. We are presenting this case because of the unusual mode of exitus.

DISCUSSION

Dr. Sally MacDonald: The autopsy findings in this case make clear the cause of death which must be attributed to mediastinal emphysema. Ham-

man[1,2] recently presented an excellent discussion of this not too well understood subject. The fact that mediastinal emphysema often complicates operations dissecting fascial planes of the neck is well known. Very frequently air in the mediastinum is associated with pneumothorax where no pleural nicking or injury is found. In these cases the pneudothorax is the result of rupture of pulmonary alveoli with the production of interstitial emphysema of the lung. The air then passes in the interstitial tissue along the course of the blood vessels to the lung hilus and then to the mediastinum. From the mediastinum the air breaks through the parietal pleura and enters the pleural cavities producing pneumothorax. Since operations on the neck are accompanied by precursor conditions of interstitial emphysema, i.e., anaesthesia, cough, tracheal or bronchial obstruction, it would seem that mediastinal emphysema following such operations is usually due to rupture of alveoli rather than direct aspiration of air into the mediastinum along the fascial planes of the neck. However, in the case at hand, there was no evidence of interstitial emphysema on microscopic sections of the lung. After tonsillectomy subcutaneous emphysema in the neck may occur and occasionally mediastinal emphysema follows. Similar episodes have been reported after irrigation of the maxillary antrum, or in association with deep wounds of the neck and wounds of the pharynx and buccal cavity. It would seem likely that air reached the mediastinum in this instance by the less common route, via the fascial planes of the neck.

Perforations of the lower part of the trachea, bronchus or esophagus may produce mediastinal emphysema. Perforation of the esophagus occurs as a result of disease processes such as erosion of mediastinal glands and in such cases the symptoms of infection are likely to over-shadow the symptoms of chronic perforation. Foreign body, trauma or operative complications of lobectomy or pneumonectomy may cause mediastinal emphysema.

Air passing along the connective tissue of the retroperitoneal space dissecting a route along the aorta or esophagus may produce emphysema of the mediastinum. Perforation of the gastro-intestinal tract, or pneumoperitoneum may be complicated by such a dissecting emphysema.

Frequently alveoli lying on interstitial bands of connective tissue rupture. Air entering the interstitial connective tissue of the lung then travels along the course of the arteries to the hilus of the lung and the mediastinum. Circumstances producing interstitial emphysema of the lungs may result from trauma to the chest, with or without fracture of the ribs, or operations on the chest, particularly the induction of pneumothorax. An increase of intra-pulmonary pressure as the result of straining with the glottis closed, heavy lifting, straining at stool, childbirth and attempts to resuscitate the newborn may cause rupture of alveoli. Partial or complete

occlusion of the trachea or bronchi usually accompanied by cough may result from insufflation anaesthesia, asthma, bronchitis, foreign bodies, whooping cough or pneumonia. Rupture of alveoli may occur spontaneously. In such instances an inherited defect of the alveoli has been postulated.

Why, in some instances of mediastinal emphysema, air remains confined to the mediastinum whereas in others it discovers an exit is not completely known. Factors governing the escape of air from the mediastinum include the pressure, which is determined by the amount of air, and the location of the air. The paths followed by air escaping from the mediastinum are: (1) by way of the subcutaneous and deep tissues of the neck; (2) through the diaphragm, about the aorta and esophagus to the retroperitoneal tissues; (3) to the pleural cavities. Air from the mediastinum frequently enters the pleural cavities, but air from the pleural cavity never enters the mediastinum. Whenever subcutaneous emphysema in the neck and pneumothorax exist together, it is probable that both are secondary to mediastinal emphysema.

As mediastinal pressure increases veins collapse and decreased inflow of blood to the heart produces dyspnea, cyanosis, and ensuing pulmonary edema may lead to death. The clinical manifestations of mediastinal emphysema may be tabulated as follows:

1. Substernal pain which is the result of distension and dissection of mediastinal tissues with possible radiation to the arms. Associated sense of oppression accompanying pain ascribed to interference with coronary circulation.

2. Obliteration of cardiac dullness.

3. Sounds heard over the heart: crackles, bubbles or churning sounds with systolic accentuation.

4. Subcutaneous and retroperitoneal emphysema symptoms of increased mediastinal pressure are inversely proportional to the extent of subcutaneous emphysema.

5. Evidence of increased mediastinal pressure: dyspnea, cyanosis, engorged veins, circulatory failure.

6. Pneumothorax.

7. X-ray evidence of air in the mediastinum.

A small amount of air in the mediastinum is soon absorbed, but when pressure in the mediastinum rises, it becomes necessary to provide exit for the air. The desired result may be obtained by deep incision into the mediastinum through the jugulum. Application of suction or a catheter introduced into the incision facilitates the escape of air. The use of a syringe and a specially curved large bore needle has on occasion brought air out so forcibly that the plunger of the syringe has been ejected. Appro-

priate treatment of tension pneumothorax consists in frequent aspirations of the pleural cavity or constant maintenance of atmospheric pressure. This may be done by introducing a needle attacked to a piece of rubber tubing, the other end of which is inserted into a bottle of water. In one case of mediastinal emphysema, occurring as a sequence to interstitial emphysema of the lungs, the mediastinum was incised through the jugulum and then induced pneudothorax was employed to collapse the injured lung.

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